Leading articles

Leptin and puberty

Our knowledge of the potential genetic link between fat metabolism and the reproductive axis dates back to the 1950s when the obese (*ob*/*ob*) mouse strain was first described. These mice were not only distinctly hyperphagic and rapidly developed obesity associated with hyperglycaemia and insulin resistance, but they were also infertile.[1] It was not until 1994 when the leptin (*ob*) gene was postionally cloned and a mutation was identified in the coding sequence of murine leptin in *ob*/*ob* mice that the cause of their obesity was recognised.[2] As predicted from the phenotype of ob/ob mice, leptin, which is principally expressed in adipocytes, had potent actions to suppress appetite and stimulate energy expenditure. It rapidly became clear that leptin could also influence the reproductive system. The sterility of male and female *ob*/*ob* mice could be reversed when recombinant leptin was administered.[3 4]

In humans, initial studies focused on the possible role that leptin may play in obesity. The hypothesis that leptin deficiency may contribute to common human obesity was soon rejected. An exponential relation between serum leptin concentration and body mass index or percentage body fat was described,[5] implying that, as a person became fatter, so insensitivity to the anorexigenic action of leptin developed. However, the relation between body fat and reproductive ability in humans has long been recognised. Both anorexia nervosa and intense physical training are associated with reduced gonadotrophin levels,[6] while Frisch had proposed that a certain amount of body fat must be accrued to achieve regular menstruation.[7] There is therefore a clear link between peripheral energy stores (in fat) and central regulation of physical development and reproductive capacity. Studies in animals and humans over the last four years have provided compelling evidence that leptin may be a neurohumoral mediator capable of signalling between the extent of nutritional intake and body fat store to the central nervous system.

Examination of the link between leptin and hypothalamic-pituitary-gonadal function has been undertaken mainly in the murine model. The relation in higher species is less well defined. In addition, the role that leptin may play in the onset of puberty, when the gonadotrophin releasing hormone (GnRH) pulse generator is being re-activated, has not been clarified. A review of data from the mouse, rat, monkey, and man and discussion of the possible neural networks involved will be presented.

The murine model

In mice, the relation between leptin and gonadal function has been tested in two situations: fasting and by direct administration of leptin. Normal mice when fasted not only develop low leptin levels as expected but also hypogonadotrophic hypogonadism, reduced thyroxine levels, and elevated adrenocorticotrophin (ACTH) and corticosterone.[8] These pituitary abnormalities could be partially reversed by leptin administered to fasted mice at a dose that returned their low leptin levels back to normal. Leptin can therefore be implicated in adaptation to starvation. Low leptin levels in times of food deprivation would result in an appetite drive, but a reduced reproductive capacity, protecting the female from conceiving and hence the energy demands of pregnancy. In addition, leptin administered to male and female ob/ob mice increased gonadotrophins (luteinising hormone in the female, follicle stimulating hormone in the male) and reproductive organ weights (ovary and uterus, testes and seminal vesicles).[9]

Intraperitoneal injections of leptin into normal mice in a dose that reduced appetite and hence body weight or in a smaller dose that had no effect on weight have been reported to bring forward the timing of normal puberty as defined by vaginal opening.[10 11] However, injections of leptin into normal prepubertal rats did not alter pubertal timing. In this model, the animals needed to be starved for an effect of leptin on puberty to be observed.[12 13] The time of first vaginal opening in leptin treated rats, with food intake reduced to 80% of normal, was similar to that in control ad libitum fed rats, with both having vaginal opening earlier than rats pair fed to the leptin group.[12] However, if the food intake in the leptin treated and pair fed control groups was restricted further down to 70% of normal, then leptin only partially reversed the delay in vaginal opening. This suggested that leptin plays a permissive rather than initiating role, allowing puberty to proceed only in favourable circumstances.

The rhesus macaque monkey

In the monkey, investigation of the role of leptin in puberty has been observational rather than interventional. In the male monkey, serum leptin levels have been measured throughout the juvenile period.[14] Leptin levels paralleled changes in testosterone, with high levels in infancy, a prepubertal nadir, then elevation through puberty. In a separate study in normal and castrated male monkeys, leptin levels were frequently monitored around the time of puberty.[15] No change in leptin concentration was found either before or during the time when luteinising hormone levels were increasing, indicating re-activation of the GnRH pulse generator and the initiation of puberty. This would imply that leptin was certainly not a trigger to puberty. Experiments in which leptin is administered to monkeys in order to assess its effect on the timing of puberty have, however, not been reported.

Human data

Data in childhood have been by necessity observational. Most studies have been cross sectional in design.[16–19] Many investigators have now reported that leptin increases gradually in both sexes over the prepubertal years. At each age, girls tend to have higher levels than boys. The leptin peak is reached at Tanner genital stage (G) 2–3 in boys, but in girls leptin continues to rise through puberty with a particular increase after menarche. In boys, leptin decreases back to early childhood levels by G5. Therefore, from late puberty and thereafter, there are strikingly discordant leptin levels between the sexes. Measures of body fatness (body mass index (BMI), BMI SD score, percentage body fat) are the most significant determinants of leptin through childhood. However, in both sexes before and during puberty (Tanner stages (TS) 1 and 2), age is a further independent determinant of leptin, implying that there is a maturational influence on leptin independent of body composition.[16] In the later stages of puberty (TS 3–5), age

remains a significant positive influence in girls, but, in boys, age is replaced by a negative effect related to increasing testicular volume. The latter is likely to reflect the inhibitory effect that testosterone has on leptin secretion. High affinity leptin binding activity, as measured by specific binding of ^{125}I-leptin in serum, varies considerably from birth through childhood. It is relatively low, at 5%, in cord blood of normal neonates, has risen to 18% at age 5, then decreases to 6% in both sexes[20] by completion of puberty. Leptin binding activity remains at the slightly higher level of 7.5% in normal adults, in whom its level does not fluctuate with age. This would suggest that leptin may become progressively more available to bind long form leptin receptors over childhood. It could then exert enhanced biological action over the period that a child is progressing towards and entering puberty.

All these data have provided further evidence that leptin has a permissive role in puberty rather than acting as a trigger. However, in one report in which leptin levels were assessed longitudinally in boys as they entered puberty, leptin appeared to show pronounced individual elevation just before the rise in testosterone.[21] This may imply a triggering role. However, other reports have not confirmed this observation.[22]

The most compelling evidence for a role for leptin in human puberty comes from those very rare families with deleterious mutations in either leptin or the leptin receptor.[23 24] In adulthood, homozygous subjects with either condition remain substantively, although not completely, hypogonadal. In a peripubertal child with leptin deficiency, treatment with leptin has led not only to pronounced effects on satiety and fat loss but also acute increases in nocturnal gonadotrophin secretion.[25] In addition, in boys with constitutional delay in growth and puberty (CDGP), a common disorder of the tempo of puberty, leptin levels at pubertal onset were lower than predicted for age and BMI.[26] In normal boys, an increase in leptin between G1 and G2 occurred as indicated above. However, leptin levels in prepubertal boys with constitutional delay in growth were not different from those in early puberty with CDGP. This suggested that the increase in leptin over the prepubertal years was not necessary to achieve puberty, but its absence was associated with a delay in entering puberty.

Leptin is clearly required for appropriate pubertal development and maintenance of secondary sexual characteristics. The combined murine and human data would infer that leptin has a permissive rather than triggering role in puberty.

Table 1 Examples of hypothalamic neurotransmitters implicated in the control of gonadotrophin releasing hormone (GnRH) neurones and/or in appetite regulation

Neurotransmitter	*GnRH regulation*	*Appetite regulation*
γ-Aminobutyric acid	Y (−)	Y (+)
Glutamate	Y (+)	Y (+)
Neuropeptide Y*	Y (− & +)	Y (+)
Galanin		Y (+)
Melanin concentrating hormone		Y (+)
Orexins		Y (+)
Leptin	Y (+)	Y (−)
CART*	Y (+)	Y (−)
Pro-opiomelanocortin*	Y (+)	Y (−)
Melanocyte stimulating hormone		Y (−)
Corticotrophin releasing hormone		Y (−)
Agouti related protein		Y (−)
Urocortin		Y (−)
Glucagon-like peptide-1		Y (−)

*Factors that may act to mediate the relation between leptin and GnRH secretion.
The sign in parentheses denotes activation/increase or inhibition/decrease.
CART, cocaine and amphetamine regulated transcript.

Leptin and hypothalamic control of GnRH

Circulating leptin is transported into the central nervous system to signal through long form receptors, located on cell bodies, such as neuropeptide Y (NPY) neurones, in the lateral hypothalamus. Many neurotransmitters and neural pathways in the hypothalamus are being linked to the control of appetite and hence body weight (table 1). Likewise, many neurotransmitters have been implicated in the control of GnRH neurones, and potentially in the control of the onset of puberty (table 1). Some of these factors affect both processes. In particular, NPY, a potent orexigenic factor and regulator of GnRH secretion, is thought to be a mediator of the central actions of leptin on appetite.[8] NPY has differing effects on GnRH secretion.[27] Both activation and inhibition have been described, depending on the model (fasted versus fed, acute versus chronic administration) and the age of the animal. In the fed and nourished state, NPY increases GnRH pulses, but in the undernourished state it inhibits GnRH neurones. In this situation, leptin levels will be low, reducing inhibition on NPY neurones. NPY levels will rise inhibiting GnRH secretion. It is not clear how these opposing actions of NPY on GnRH are mediated. Nevertheless, NPY can clearly act as a central link between nutrition and reproductive function, just as leptin fulfils this role as a peripheral factor.

Leptin also acts on cell bodies, which express cocaine and amphetamine regulated transcript (CART), another anorectic peptide. In in vitro experiments using retrochiasmatic hypothalamic explants of GnRH neurones from prepubertal female rats, leptin can stimulate CART expression, which in turn reduces the interval between pulses of GnRH secretion.[28] However, effects of NPY on GnRH pulse interval were not affected by antibodies to CART, implying that the leptin-CART pathway was independent of NPY. It is likely that a number of pathways that can link leptin through to GnRH neurones will be found.

Conclusion

There has been disappointment that leptin deficiency was not the answer to common obesity and that leptin treatment was unlikely to make a significant contribution to improving the health burden resulting from obesity. It appeared that serum leptin in adults was principally a marker of fat mass. In children, however, evidence is mounting that leptin has an important permissive role in the progression into puberty and the maintenance of normal hypothalamic-pituitary-gonadal function thereafter. The central networks in the hypothalamus that mediate this relation are complex and as yet not fully defined. Nevertheless there are neurotransmitters that impact on appetite and GnRH neurones. It will be important to understand these networks as the pharmaceutical drive to develop specific anorectic agents may have repercussions for pubertal and reproductive function.

At present the measurement of leptin in relation to puberty does not have a clinical application. However, further investigation of the exact relation between nutritional intake, body composition, growth, and development may be key to characterising mechanisms that control the tempo of growth.

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Mental health must be "centre stage" in child welfare

The size of the problem

The alarmingly high incidence of behaviour and emotional disorders in children in the United Kingdom was established 30 years ago.[1] A minimum annual incidence of 5–10% for children living in relatively stable semirural communities and 10–20% for those in inner cities was found. Recently, an overall annual national incidence of 10% has been reported.[2] Authoritative reviews suggest that there has, if anything, been a rise in the incidence of at least some of these disorders over the past 40 years.[3] Illustrative case reports have shown that, among mainly undiagnosed, young, untreated children identified with psychiatric disorders in the community, even those with less serious levels of disturbance are suffering major impairment of social functioning.[4]

The community response

Until about five years ago, the official response to these striking epidemiological findings was disappointing. From 1970 to 1995, there was a slow increase in the number of consultant posts in child and adolescent psychiatry and in the number of training positions, but the need to improve services for mental health problems in the school setting, for children receiving paediatric care, and for children in contact with social services (especially those in public care), and for young offenders was not clearly recognised, and, insofar as it was, the measures taken to improve the situation were inadequate and sometimes, as in the case of young offenders, calculated to do more harm than good.

However, in the past five years there has been a very substantial change in the attitudes of central government, beginning with the previous administration and gathering pace under the present one. The degree to which the change in attitude will be reflected in willingness to bring about improvement in the relevant structures, tackle difficult interprofessional issues, and provide increased resources is unclear, but a definite and promising start has been made. Child mental health is a great deal nearer centre stage than it was five years ago.

In 1994 Zarrina Kurtz and her colleagues published what amounted to a consumer survey of child and adolescent mental health services (CAMHS).[5] The findings were, to put it mildly, not complimentary to the service. For example, 67% of hospital paediatricians stated "their local service was woefully inadequate, very limited, overwhelmed by referrals, barely adequate, or with enormous waiting lists". Community paediatricians, who reported that a substantial amount of their work was psychiatric in nature, were reported to feel even more strongly that CAMHS resources were quite inadequate. Among social services respondents, almost a half reported that the "service was virtually nil, inadequate or limited with long waiting times". Although the opinions of family doctors were not canvassed in this survey, it is improbable that the replies would have been substantially different. For the sake of balance, it should be added that, at the same time, surveys of attendees at child psychiatric clinics suggested a reasonably high level of satisfaction.[6] The problem appeared to be the inadequacy and uneven distribution of resources rather than the quality of the service received by those who did, in fact, receive it.

Kurtz *et al*[5] made a number of recommendations including the need for more sophisticated purchasing, greater use of child psychiatrists for consultation and liaison, regular audit, and a wider and more appropriate use of community child psychiatric nurses. Interestingly, in line with the philosophy of the time, they did not mention the need for increased resources.

In 1995 the Departments of Health and Education and the Social Services Inspectorate produced a *Handbook on child and adolescent mental health*.[7] This document introduced the concept of a tiered CAMHS, proposed earlier by P Hill (personal communication, 1999), with tier 1 providing primary care, tier 2 being represented by uniprofessional groups relating to others through a network, tier 3 providing a locally accessible specialist service, and tier 4 a more specialist service for children with unusual needs. In the same year, the NHS Executive commissioned a thorough *Health care needs assessment in child and adolescent mental health*,[8] and the health advisory service produced a substantial document entitled *Together we stand* giving guidance on the commissioning, role, and management of CAMHS.[9]

In 1997, the House of Commons select committee on health produced a *Report on child and adolescent mental health services*,[10] which noted that "the current provision of child and adolescent services is inadequate both in quality and in geographical spread", and supported the four tier model of services. In 1999, the Mental Health Foundation published the report of a committee of enquiry chaired by Tessa Baring, entitled *Bright futures: promoting children and young people's mental health*.[11] The title of this annotation is taken from that report. In the same year the Audit Commission, whose brief is to promote the best use of public money, came out with *Children in mind*,[12] a report on CAMHS which disclosed that there was as much as a sevenfold difference in CAMHS resources in different parts of England and Wales.

This volume of attention given to CAMHS is impressive, but, as Dr Seuss's cat in the hat[13] exclaimed, that is not all, that is not all! Various other relevant government initiatives and reports must be cited, including: Home Office legislation on young offenders setting up multiagency youth offending teams; Department for Education and Employment (DfEE) guidance on reducing the risk of disaffection among pupils by, for example, rewarding achievement, supporting behaviour management, and working with parents[14]; "Quality protects", a Department of Health programme setting standards for the care of children in public care as well as draft guidance from the same source on the multidisciplinary management of child abuse,[15] and a report from the Social Exclusion Unit on children excluded from school.[16]

The attention given to child mental health problems and CAMHS over the past five years is staggering. But what, if anything, has really happened to improve the lot of children suffering from behaviour and emotional disorders? What has occurred to help those in non-CAMHS professions, such as paediatricians, to deal more effectively with such children?

Here there is inevitably less positive information, but nevertheless it would be ungrateful to fail to note really noteworthy progress. The approach that the present administration has taken is largely, but not exclusively, to put extra resources into non-CAMHS services that can be seen as preventive in relation to the development of mental health problems.

Prevention: relevant government initiatives

None of the preventive initiatives that the government has set in train have been given a specific mental health "spin".